DOI:10.1111/j.1477-2574.2011.00326.x

ORIGINAL ARTICLE

Refining the definition of perioperative mortality following hepatectomy using death within 90 days as the standard criterion

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Abstract

Objectives: Defining perioperative mortality as death that occurs within 30 days of surgery may underestimate 'true' mortality among patients undergoing hepatic resection. To better define perioperative mortality, trends in the risk for death during the first 90 days after hepatectomy were assessed.

Methods: Surveillance, Epidemiology and End Results (SEER) Medicare data were used to identify 2597 patients who underwent hepatic resection during 1991–2006. Data on their clinicopathological characteristics, surgical management and perioperative mortality were collected and survival was assessed at 30, 60 and 90 days post-surgery.

Results: Overall, 5.7% of patients died within the first 30 days. Postoperative mortality at 60 and 90 days were 8.3% and 10.1%. In-hospital mortality after hepatic resection was greater among patients with hepatocellular carcinoma (HCC) than among those with colorectal liver metastases (CRLM) (8.9% and 3.8%, respectively; $P < 0.001$). In CRLM patients, mortality increased from 4.3% at 30 days to 8.4% at 90 days, whereas mortality in HCC patients increased from 9.7% at 30 days to 15.0% at 90 days (both $P < 0.05$). Patients with HCC were twice as likely as CRLM patients to die within 30 days [odds ratio (OR) 2.03], 60 days (OR = 1.74) and 90 days (OR = 1.71) (all $P < 0.001$). Differences in 30- and 90-day mortality were greatest among HCC patients undergoing major hepatic resection ($P < 0.05$).

Conclusions: Reporting deaths that occur within a maximum of 30 days of surgery underestimates the mortality associated with hepatic resection. Traditional 30-day definitions of mortality are misleading and surgeons should report all perioperative outcomes that occur within 90 days of hepatic resection.

Keywords

hepatectomy, mortality, surgery, SEER (Surveillance, Epidemiology and End Results), Medicare, survival

Received 1 March 2011; accepted 8 April 2011

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Introduction

Hepatic resection, alone or in combination with ablative techniques, has increased over the past decade in patients with primary hepatic or secondary metastatic lesions.[1–4] In the USA, the two most common indications for hepatic resection of a malignant lesion are hepatocellular carcinoma (HCC) and colorectal liver metastasis (CRLM).[3] Improvements in patient risk factor modification, operative techniques and perioperative management have resulted in perioperative mortality rates of <1% in high-volume hepatobiliary centres[5] and 5–10% in population-based analyses using administrative data.[4] Traditionally, patient mortality at 30 days has been used as a benchmark to assess the quality of both hospital and surgeon performance in virtually all major surgical procedures, including hepatic resection. As hepatobiliary surgeons continue to expand the pool of operable candidates by using techniques such as resection combined with ablation,[6] portal vein embolization[7] and two-stage hepatectomy,[8] the potential risk for postoperative hepatic insufficiency and

This paper was presented at the American Hepato-Pancreato-Biliary Association 11th Annual Meeting, Miami, FL, USA.

therefore late mortality increases. Mortality associated with hepatic insufficiency may not be accurately captured in traditional 30-day measures of mortality because of the variance of hepatic parenchymal regeneration after resection, which depend on several factors, including the presence of underlying disease such as cirrhosis or steatohepatitis.[9]

Most reports on mortality following hepatectomy for HCC or CRLM come from large, single-institution series.[1,10–15] Clinical risk factors in patients with HCC often differ from those in patients with CRLM, which makes it difficult to interpret data from studies that report aggregate institutional perioperative mortality. In addition, data from 'centres of excellence' may be subject to referral and reporting bias. Large, population-based studies assessing the patterns of care and mortality in patients undergoing hepatectomy have been limited by the use of only administrative databases such as the National Inpatient Sample (NIS) and have included patients without an oncological reason for hepatic resection.[3,4,16,17] By contrast, the Surveillance, Epidemiology and End Results (SEER) Cancer Registry provides patient- and primary tumour-specific data, information about the utilization of perioperative services and data on patient outcomes. When SEER data are linked with Medicare data, detailed claims-derived data on the provision of services to beneficiaries become available, which allows for better risk-adjusted analyses. In turn, the use of the linked SEER–Medicare database allows for a more accurate examination of procedure utilization and patient outcomes that can more readily be extrapolated to the US population at large.[18] The objective of the current study was to evaluate traditional 30-day mortality relative to 90-day mortality. Specifically, its goal was to quantitate the potential relative under-reporting of hepatectomy-associated mortality by assessing the incremental increase in mortality noted at 90 days in a cohort of patients with CRLM or HCC within a SEER–Medicare linked dataset over a 16-year period. The study hypothesis presumed that the inclusion of perioperative deaths occurring up to 90 days following surgery would provide a more accurate estimate of hepatectomy-associated mortality in the perioperative period.

Materials and methods

Data source

Prospectively collected data from the linked SEER–Medicare database were utilized. Taken together, these data represent the linking of two large, population-based sources of data and provide detailed information about Medicare beneficiaries with cancer. The SEER database is maintained by the National Cancer Institute (NCI)[19] and its characteristics have been well described in prior reports.[20] The SEER programme of cancer registries collects clinical, demographic and cause-of-death information for persons with cancer. The SEER–Medicare data represent a linking of SEER data to Medicare claims data for health care services covered from the time of Medicare eligibility until death.[21] These linked data are available from 1991 and the SEER–Medicare database has successfully matched data for 93% of individuals aged ≥65 years at the time of primary cancer diagnosis to their Medicare enrolment files. Available data include information on the original surgical resection in addition to any perioperative procedural interventions in either inpatient or outpatient settings around the time of the operation.

Case definitions

All Medicare-enrolled patients aged ≥65 years who were diagnosed with incident malignant primary colorectal adenocarcinoma or HCC between 1991 and 2006 were evaluated for inclusion. Patients with colorectal adenocarcinoma (CRC) or HCC were identified according to International Classification of Diseases for Oncology (ICD-O-3) topography, behaviour and histology codes.[22] Patients with CRC were included if they had topography codes representative of primary tumours located in the caecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon, large intestine, not otherwise specified, rectosigmoid junction or rectum, as well as a code indicative of malignant behaviour. For patients with CRC, histology codes were selected to identify only patients with adenocarcinoma; patients with other histology codes (such as for carcinoid histology, etc.) were excluded. A gastrointestinal pathologist at Johns Hopkins Hospital (RAA) reviewed all histology codes to determine which codes were relevant to CRC or HCC. Patients with primary CRC and hepatic metastases were identified using an established algorithm[23] that employed the ICD, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes and Current Procedural Terminology (CPT) codes for malignant neoplasm of liver, secondary malignant neoplasm of liver, hepatectomy and ablation of liver lesion or tissue. Patients who underwent only ablations of CRLM or HCC were excluded from this analysis. The study cohort included only patients enrolled in both Medicare Parts A and B who were not enrolled in a managed care plan during the study period. The SEER–Medicare datasets for HCC and CRLM patients were combined for analysis.

Outcome and predictor variables

Previous studies have demonstrated the validity of Medicare billing codes to assess a wide range of outcomes.[24] Information on age, gender, race, marital status and geographic region were obtained from the SEER portion of the database. Variables were transformed into categorical and indicator variables where appropriate. The Elixhauser Comorbidity Index, a comprehensive set of 30 comorbidity measures, was used to identify and adjust for comorbid conditions.[25–29] Comorbid diagnoses related to the patient's admission diagnosis (e.g. metastatic cancer), as well as any comorbid condition with a frequency of <5, were excluded so that a total of 20 comorbidities remained for analysis.

Statistical analyses

Median values with ranges were used to describe continuous data; discrete variables were displayed as totals and frequencies. Cells with fewer than 11 patients per variable cell were re-labelled as

'<11 (<X.x%)' in compliance with the NCI regulation for reporting of SEER–Medicare data. Univariate comparisons were assessed using the two-sample Student's *t*-test or the Mann–Whitney *U*-test for continuous variables and the chi-squared test for dichotomous and categorical variables where appropriate. For the purposes of analysis, the distribution of the total number of comorbid conditions per patient was transformed into a categorical variable representing either up to two comorbidities or more than two comorbidities. Cumulative event rates were calculated using the method of Kaplan and Meier[30] and survival curves were compared using the log-rank test. Survival time was calculated from the date of the liver-directed operation to the time of interest (e.g. 30 days or 90 days). In-hospital death was defined as patient survival less than the total length of hospital stay after the liver-directed operation. Multivariate logistic regression models were constructed for patients who died within 30 days and within 90 days of surgery. In order to identify variables for inclusion in the multivariate model, variables were selected using a univariate significance of $P < 0.25$ in combination with important clinical variables and confounders. The Hosmer–Lemeshow goodness-of-fit test and a receiver operating characteristic (ROC) curve were used to evaluate the model's performance and discriminative ability. Significance levels were set at $P < 0.05$; all tests were two-sided. All statistical analyses were performed using SPSS Version 18.0 (SPSS, Inc., Chicago, IL, USA).

Results

Characteristics of the entire cohort

The demographic and clinical characteristics of the patient cohort are outlined in Table 1. In total, 2597 patients were identified for analysis. The majority of patients had CRLM (n = 1903, 73.3%) rather than HCC (n = 694, 26.7%). The median number of

Table 1 Demographic, clinical, and operative characteristics of patients with colorectal liver metastasis (CRLM) or hepatocellular carcinoma (HCC) undergoing hepatectomy during 1991–2006

Variable	Total, *n* (%) (*n* = 2597)	CRLM, *n* (%) (*n* = 1903)	HCC, *n* (%) (*n* = 694)	*P*-value[a]
Demographics				
Median age at hepatectomy, years (range)	73.0 (65–98)	73.0 (65–98)	73.0 (65–92)	0.018
Male	1423 (54.8)	973 (51.1)	450 (64.8)	<0.001
White race	2073 (79.8)	1624 (85.3)	449 (64.7)	<0.001
Married	1684 (64.8)	1221 (64.2)	463 (66.7)	0.228
Urban	2407 (92.7)	1756 (92.3)	651 (93.8)	0.186
Primary tumour characteristics				
Grade				
Well-differentiated	292 (11.2)	119 (6.3)	173 (24.9)	<0.001
Moderately differentiated	1533 (59.0)	1285 (67.5)	248 (35.7)	<0.001
Poorly differentiated	499 (19.2)	396 (20.8)	103 (14.8)	<0.001
Undifferentiated	36 (1.4)	18 (0.9)	18 (2.6)	0.001
Unknown	237 (9.1)	85 (4.5)	152 (21.9)	0.001
Elixhauser comorbidities				
Median number of comorbidities (SD)	2.0 (1.9)	2.0 (1.8)	3.0 (2.0)	<0.001
Operative details				
Year of hepatectomy				
1991–2000	1320 (50.8)	1012 (53.2)	308 (44.4)	<0.001
2001–2006	1277 (49.2)	891 (46.8)	386 (55.6)	<0.001
Hepatectomy alone	2295 (88.4)	1696 (89.1)	599 (86.3)	0.048
Hepatectomy and ablation	302 (11.6)	207 (10.9)	95 (13.7)	0.048
Type of hepatic resection				
Partial hepatectomy only (wedge)	1551 (59.7)	1242 (65.3)	309 (44.5)	<0.001
Hemihepatectomy	1046 (40.3)	661 (34.7)	385 (55.5)	<0.001
Extended hepatectomy	117 (4.5)	66 (3.5)	51 (7.3)	<0.001
Median length of stay, days (SD)	7.0 (8.5)	7.0 (7.4)	8.0 (11.1)	0.080

[a]All statistical tests were performed with 1 degree of freedom (d.f.)
SD, standard deviation

Table 2 Perioperative mortality in patients with operatively managed colorectal liver metastasis (CRLM) (n = 1903) or hepatocellular carcinoma (HCC) (n = 694) who died at ≤30 days, ≤60 days or ≤90 days of the liver-directed operation

Variable	Total, n (%) (n = 2597)	CRLM, n (%) (n = 1903)	HCC, n (%) (n = 694)	P-value[a]
In-hospital mortality	135 (5.2)	73 (3.8)	62 (8.9)	<0.001
Death at ≤30 days	148 (5.7)	81 (4.3)	67 (9.7)	<0.001
Death at ≤60 days	215 (8.3)	128 (6.7)	87 (12.5)	<0.001
Death at ≤90 days	263 (10.1)	169 (8.4)	104 (15.0)	<0.001

[a]All statistical tests were performed with 1 degree of freedom (d.f.)

Elixhauser medical comorbidities was 2.0 (range: 0–11). The most common medical comorbidities were cardiac arrhythmias (n = 564, 21.7%), peripheral vascular disorders (n = 338, 13.0%) and congestive heart failure (n = 319, 12.3%). Out of the entire cohort, 49.2% of patients (n = 1277) underwent hepatectomy during 2001–2006 and the majority of patients underwent hepatectomy alone (n = 2295, 88.4%). The use of combined hepatectomy + ablation was restricted to 11.6% of the overall patient cohort (n = 302). In terms of the type of hepatic resection, 40.3% (n = 1046) of patients were managed with a hemihepatectomy, whereas an extended hepatectomy was utilized in 4.5% of patients (n = 117). The median overall length of stay following the operation was 7.0 days (range: 0–220 days).

Patient and primary tumour characteristics: CRLM vs. HCC

Given the known clinicopathological differences between patients with HCC and CRLM, the data were stratified by cancer histology (Table 1). As expected, numerous differences emerged between patients with HCC and those with CRLM. Importantly, patients with HCC had a greater median number of medical comorbidities (3.0; range: 0–10) compared to patients with CRLM (2.0; range: 0–11) (P < 0.001). Patients with HCC were more likely to have an Elixhauser comorbidity indicating liver dysfunction than patients with CRLM (n = 309, 44.5% and n = 84, 4.4%, respectively; P < 0.001).

Operative details: CRLM vs. HCC

Patients with HCC were more likely to have undergone hepatic resection in the later years of the study compared with patients with CRLM (n = 386, 55.6% and n = 891, 46.8% for years 2001–2006; P < 0.001). A combined modality approach of hepatectomy + ablation was employed more frequently in patients with HCC than those with CRLM (n = 95, 13.7% and n = 207, 10.9%, respectively; P = 0.048). Whereas patients with CRLM more often underwent a partial hepatectomy only (i.e. wedge resection) (n = 1242, 65.3% vs. n = 309, 44.5%), patients with HCC were more likely to have undergone a hemihepatectomy (n = 385, 55.5% vs. n = 661, 34.7%) (all P < 0.001). There was no difference in the median length of stay between patients with HCC and those with CRLM (P = 0.080).

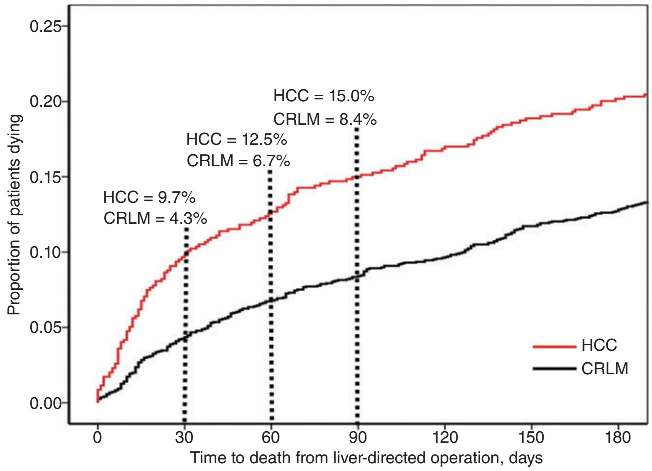

Figure 1 Time to perioperative death after hepatic resection in patients with colorectal liver metastasis (CRLM) or hepatocellular carcinoma (HCC), showing the proportions of deaths occurring by 30, 60 and 90 days (n = 2597)

Perioperative mortality

Overall, in-hospital mortality among all patients was 5.2% (n = 135) (Table 2). Patients with HCC incurred more than twice the in-hospital mortality suffered by patients with CRLM (8.9% vs. 3.8%; P < 0.001). There was no difference in 30- or 90-day mortality with respect to the year of hepatectomy (both P > 0.05 for 1991–2000 compared with 2001–2006). Differences in death rates between patients with CRLM and those with HCC varied greatly at 30, 60 and 90 days (all P < 0.001). Overall, 148 deaths (5.7%) occurred by 30 days and an additional 115 deaths (representing 43.7% of all deaths) occurred between 30 and 90 days. In the CRLM patient group, 81 deaths (4.3%) occurred by 30 days and 169 (8.4%) occurred by 90 days (Fig. 1). Similarly, in patients with HCC, 67 deaths (9.7%) occurred by 30 days and 104 (15.0%) occurred by 90 days. For patients with CRLM, assessing deaths at 90 days increased the perioperative mortality rate by >50% (n = 81 to n = 169) (Fig. 2). There was a similar difference between mortality rates at 30 and 90 days in HCC patients, which increased by 36% from 67 at 30 days to 104 at 90 days.

As shown in Fig. 2, the slope of the curves representing the incremental risk for death was steepest for both HCC and CRLM

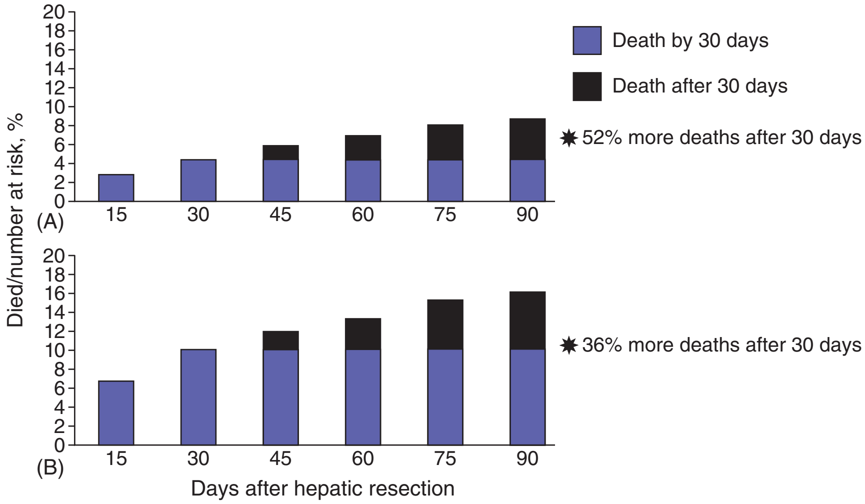

Figure 2 Trends in 90-day mortality after hepatectomy in patients with (A) colorectal liver metastasis (CRLM) or (B) hepatocellular carcinoma (HCC)

patients within the first 30 days following hepatic resection (HCC = 0.32% dead/day; CRLM = 0.14% dead/day). Of note, the risk for death after hepatectomy for HCC and CRLM was 0.09% dead/day at 30 days and 0.07% dead/day at 90 days. The curves for both groups attained a relatively constant slope from day 90 that was maintained at a relatively constant rate throughout the first year (HCC = 0.08% dead/day; CRLM = 0.06% dead/day).

Factors associated with survival at 30 and 90 days

In assessing the entire study cohort, on univariate analysis the risk for death at <30 days was associated with diagnosis of HCC, more than two Elixhauser medical comorbidities, and resection ≥ hemihepatectomy (all $P < 0.05$). When the risk for death was stratified by clinical diagnosis, among patients with CRLM the risk for death within 30 days of surgery was associated with age and an increased number of comorbidities. Similarly, among patients with HCC, mortality within 30 days was associated with increased age and male gender, but not with the number of Elixhauser comorbidities (Table 3). On multivariate logistic regression analysis (Table 4), the risk for death by 30 days remained associated with a diagnosis of HCC [odds ratio (OR) 2.03, 95% confidence interval (CI) 1.42–2.88; $P < 0.001$], more than two Elixhauser medical comorbidities (OR = 1.61, 95% CI 1.14–2.27; $P = 0.007$), and resection ≥ hemihepatectomy (OR = 1.53, 95% CI 1.08–2.16; $P = 0.016$). There was an incremental increased risk for death by 90 days with a diagnosis of HCC (OR = 1.71, 95% CI 1.29–2.26; $P < 0.001$), more than two Elixhauser medical comorbidities (OR = 1.49, 95% CI 1.14–1.94; $P = 0.003$), and resection ≥ hemihepatectomy (OR = 1.37, 95% CI 1.05–1.79; $P = 0.019$). After controlling for other factors, patients with HCC were twice as likely as those with CRLM to die within 30 days (OR = 2.03), 60 days (OR = 1.74) or 90 days (OR = 1.71) (all $P < 0.001$). Differences in 30- and 90-day mortality were greatest among HCC patients undergoing major hepatic resection ($P < 0.05$) (Fig. 3).

Discussion

Even as recently as the 1980s, perioperative mortality associated with hepatectomy was reported to be as high as 10–20%.[10,11,31] Major hepatectomy was often associated with substantial blood loss and varying degrees of hepatic insufficiency or failure. Over the past several decades, however, mortality associated with hepatic resection has decreased significantly.[2,13,32,33] The reason for this decrease in reported mortality is probably multi-factorial and related, in part, to improvements in perioperative care, better patient selection and improvements in operative techniques. Like data reported for most other major surgical procedures, hepatectomy-associated mortality has traditionally been reported as any in-hospital death or death occurring within 30 days of the surgical procedure. The reporting of death within this timeframe was sufficient when the causes of perioperative death (e.g. substantial blood loss) transpired in a relatively short time. However, operative techniques and methods to expand the number of operative candidates (e.g. portal vein embolization, two-stage hepatectomy, etc.) have changed, mandating a reconsideration of what actually constitutes perioperative mortality. In parallel with growing understanding of how liver insufficiency and liver failure impact on mortality rates by causing 'late' deaths, there has been a push toward the routine reporting of all deaths within 90 days of hepatic resection. In fact, postoperative liver failure can occur in as many as 15% of patients, ultimately accounting for >60% of postoperative deaths.[34] Although some major hepatobiliary centres now routinely report 90-day mortality,[34,35] operative mortality is still frequently reported in the literature based on in-hospital deaths only[3] or events occurring within 30 days.[1,36,37]

Table 3 Clinicopathological characteristics of patients with colorectal liver metastasis (CRLM) (n = 1903) or hepatocellular carcinoma (HCC) (n = 694) who died at ≤30 days, ≤60 days or ≤90 days and the univariate risk for death at < 30 days compared with ≥30 days

Patients with CRLM	Death at ≤30 days, n (%) (n = 81)	Death at ≤60 days, n (%) (n = 118)	Death at ≤90 days, n (%) (n = 159)	OR[a]	95% CI	P-value
Percentage of all CRLM patients	4.3	6.2	8.4	–	–	–
Year of hepatectomy						
1991–2000	47 (58.0)	76 (59.4)	86 (54.1)	1.23	0.78–1.93	0.373
2001–2006	34 (42.0)	32 (40.6)	73 (45.9)		*(Referent)*	
Median age at hepatectomy, years	77.0	77.0	77.0	1.08	1.04–1.16	<0.001
Male gender	43 (53.1)	78 (60.9)	94 (59.1)	1.09	0.70–1.70	0.719
White race	72 (88.9)	110 (85.9)	137 (86.2)	1.39	0.69–2.82	0.358
Elixhauser comorbidities						
0–2 comorbidities	43 (53.1)	71 (55.5)	87 (54.7)		*(Referent)*	
>2 comorbidities	38 (46.9)	57 (44.5)	72 (45.3)	1.90	1.21–2.97	0.005
Resection ≥ hemihepatectomy	34 (42.0)	51 (39.8)	59 (37.1)	1.38	0.88–2.17	0.163
Hepatectomy and ablation	<11 (<13.6)	11 (8.6)	14 (8.8)	0.53	0.21–1.32	0.172
Patients with HCC	**(n = 67)**	**(n = 87)**	**(n = 104)**	**OR[a]**	**95% CI**	**P-value**
Percentage of all HCC patients	9.7	12.5	15.0	–	–	–
Year of hepatectomy						
1991–2000	27 (40.3)	32 (36.8)	39 (37.5)	0.83	0.50–1.39	0.480
2001–2006	47 (59.7)	55 (63.2)	65 (62.5)		*(Referent)*	
Median age at hepatectomy, years	75.0	75.0	75.0	1.05	1.01–1.09	0.032
Male gender	36 (53.7)	48 (55.2)	68 (65.4)	0.60	0.36–0.99	0.047
White race	45 (67.2)	56 (64.4)	68 (65.4)	1.13	0.66–1.93	0.657
Elixhauser comorbidities						
0–2 comorbidities	27 (35.8)	37 (42.5)	44 (42.3)		*(Referent)*	
>2 comorbidities	40 (59.7)	50 (57.5)	60 (57.7)	1.37	0.82–2.28	0.231
Resection ≥ hemihepatectomy	43 (64.2)	55 (63.2)	67 (64.4)	1.49	0.89–2.52	0.133
Hepatectomy and ablation	<11 (<16.4)	14 (16.1)	18 (17.3)	1.12	0.55–2.28	0.757

As per the National Cancer Institute data usage agreement, no cells with totals of <11 were reported
All statistical tests were performed with 1 degree of freedom (d.f.)
[a]The OR is the univariate risk for death at ≤30 days compared with >30 days
OR, odds ratio; 95% CI, 95% confidence interval

Table 4 Multivariate logistic regression analyses of factors associated with risk for death by 30 days compared with by 90 days in patients undergoing liver-directed surgery for management of colorectal liver metastasis (CRLM) or hepatocellular carcinoma (HCC)

Prognostic factor	Death at ≤30 days			Death at ≤90 days		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
HCC	2.03	1.42–2.88	<0.001	1.71	1.29–2.26	<0.001
Age >73 years	1.54	1.09–2.18	0.014	1.91	1.46–2.50	<0.001
>2 comorbidities	1.61	1.14–2.27	0.007	1.49	1.14–1.94	0.003
Resection ≥ hemihepatectomy	1.53	1.08–2.16	0.016	1.37	1.05–1.79	0.019

All statistical tests were performed with 4 degrees of freedom (d.f.)
OR, odds ratio; 95% CI, 95% confidence interval

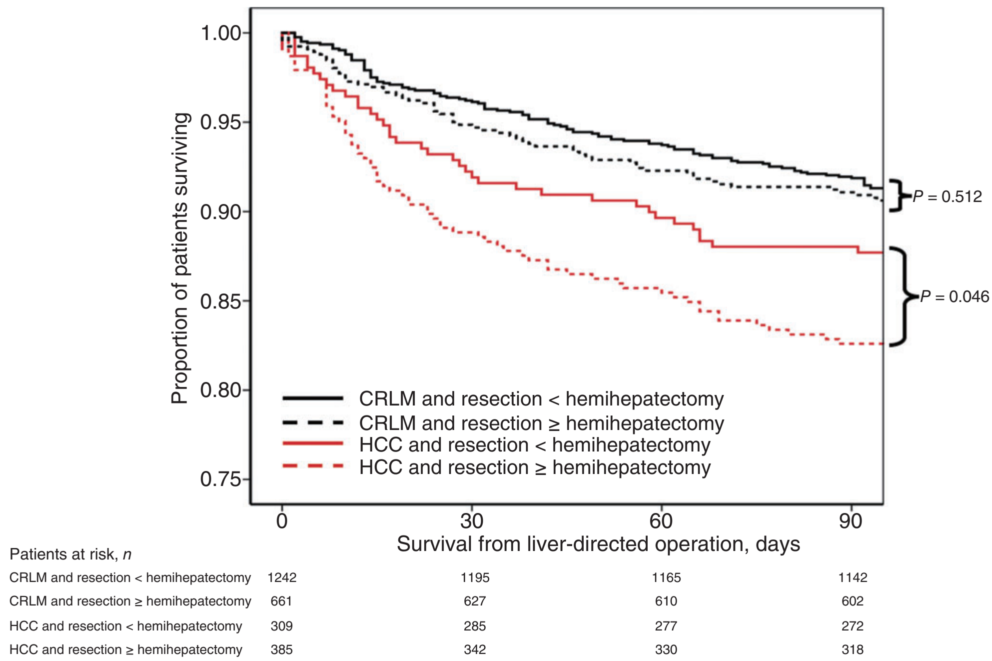

Figure 3 Survival in patients with colorectal liver metastasis (CRLM) or hepatocellular carcinoma (HCC) stratified by extent of liver resection (*n* = 2597)

Perhaps more interestingly, despite the emerging consensus among liver surgeons to report 90-day outcomes, there is a paucity of data that actually quantify the potential relative underestimation of hepatectomy-associated mortality caused by reporting 30- rather than 90-day mortality. The current study is important because it provides an empirical, quantitative benchmark of how many hepatectomy-associated deaths are 'missed' by the reporting of only in-hospital and 30-day outcomes. In addition, unlike many previous studies, the SEER–Medicare dataset was utilized. This allowed the reporting of more generalizable population-based statistics, as well as disease-specific data regarding indications for hepatic resection (e.g. CRLM vs. HCC).

In the current study, overall hepatectomy-associated in-hospital mortality was 5.2%, which is similar to rates previously reported from other datasets such as the NIS.[4,16] The NIS, however, may be particularly poorly suited to estimate mortality associated with hepatectomy as it contains only inpatient data and does not allow mortality to be tracked longitudinally. As such, most population-based data on hepatectomy-associated mortality are limited to the inpatient setting. By contrast, the linked SEER–Medicare dataset allows hepatectomy-associated mortality to be estimated over a longer period of time from the index procedure. Accordingly, in-hospital and 30-day mortality rates were found to be similar (5.2% vs. 5.7%, respectively). Carroll *et al.*[38] noted that in-hospital and 30-day mortality rates after resection of pancreatic cancer were similar, which suggested that comparisons of mortality rates utilizing either of these metrics were acceptable. Perhaps of more importance were findings regarding the incremental death events noted between days 30 and 90 following hepatic resection. Specifically, of the 263 (10.1%) perioperative deaths in the cohort, almost half (n = 115, 43.7%) occurred between days 31 and 90. As such, 30-day mortality would have significantly underestimated the 'true' incidence of perioperative death associated with hepatic surgery. Assessing deaths at 90 days increased the perioperative mortality rate by >50% (from 4.3% at day 30 to 8.4% at day 90) in CRLM patients and by 36% (9.7% at day 30 to 15.0% at day 90) in HCC patients undergoing liver resection (Fig. 2). Rates of death in patients with HCC or CRLM were also noted not to become relatively constant until 90 days. In aggregate, these data strongly suggest that a 30-day cut-off to report operative mortality for hepatic resection is inappropriate as it underestimates the 'true' operative risk by about 50%.

Although most cancer care in the USA does not take place at specialized cancer centres, the literature concerning perioperative mortality following hepatectomy is most commonly derived from large, single-institution series.[1,34,35,39,40] The authors of the current study have previously reported that actual population-based mortality for liver resections may indeed be higher than rates reported in the literature. In fact, the authors demonstrated that mortality following liver surgery based on data derived from the NIS dataset was 1.5 times higher than mortality reported from single-centre experiences. The current work corroborates and expands on previous findings reported by its authors. Using the SEER–Medicare dataset resulted in the demonstration of overall mortality rates of 5.2% at 30 days and 10.1% at 90 days. These mortality figures stand in stark contrast with most mortality data published from single-institution series, which have routinely reported the incidence of postoperative deaths to be <2% or even zero.[39,41–43] Although the reason for these disparate mortality figures is probably multi-factorial, the self-reporting of institutional data has previously been shown to be susceptible to reporting bias.[16,44,45] Population-based studies, such as the current study, are therefore important as the data are more reflective of the mortality associated with hepatectomy at the national – rather than local or regional – level.

In addition to urging the reporting of mortality data based on 90-day outcomes, the data presented in this report imply that such data should be stratified by both operative indication and extent of hepatic resection. Many single-institution series and population-based studies have reported aggregate data on hepatic resection, irrespective of either clinical diagnosis or extent of hepatic resection.[3,4,9,16,39,46] As demonstrated in the current study, however, the clinical risk profiles of patients with HCC differed significantly from those of patients with CRLM, resulting in an almost two-fold increase in 30- and 90-day mortality (Fig. 2). Depending upon the referral practices of a particular institution, the case mix of patients undergoing hepatic resection for HCC compared with those undergoing the same procedure for CRLM may vary considerably across institutions. In addition, resection ≥ hemihepatectomy was noted to be associated with an increased risk for death by 90 days of about 40% (Fig. 3). As such, the reporting of aggregate perioperative hepatectomy-associated mortality data would seem to be inadequate and potentially misleading. In an era scrutinized for optimal outcomes and characterized by pay-for-performance policies,[47] the present data indicate that hepatectomy-associated mortality should be stratified by both indication and type of hepatic surgery when comparing different institutions.

The current study has several limitations. Although the SEER–Medicare dataset allows for the examination of mortality in a longitudinal manner, it does not provide data on the exact cause of death. As such, data on the cause of death following hepatectomy were lacking and it was not possible to evaluate the impact of liver insufficiency or failure relative to other causes of death. The objective of the study was, however, not to examine disease-specific death, but, rather, to establish the relative differences in overall 30- and 90-day mortality rates. In addition, because this study utilized a dataset linked to Medicare, only patients aged ≥65 years were included. In general, this limitation would not necessarily seem to impact on the main findings and conclusions of the study. However, it is possible that results from the current study might have differed in a younger patient population with or without similar comorbidities and this should be taken into account in their consideration.

In conclusion, the traditional use of 30 days as a cut-off when reporting mortality in patients undergoing hepatectomy for malignancy is inadequate. Mortality based only on data known at 30 days is misleading and greatly underestimates actual perioperative mortality by up to 50%. Although the slope of the curve representing the incremental risk for death is steepest within the first 30 days following hepatic resection, it continues to rise for the period between 30 and 90 days and does not attain a relatively constant slope until after 90 days. In addition, given that patients with HCC and CRLM empirically have differing clinicopathological risk factors, institutional data on perioperative mortality should be stratified by indication and the extent of resection. Accurate information on perioperative mortality associated with liver surgery is critical to gaining proper patient consent, as well as for accurate risk assessment and stratification. Data from the current study clearly and unequivocally establish 90-day mortality as the standard metric for reporting mortality data following hepatic resection.

Conflicts of interest

None declared.

References

1. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. (1999) Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 230:309–318; discussion 318–321.
2. Jarnagin WR, Gonen M, Fong Y, DeMatteo RP, Ben-Porat L, Little S *et al*. (2002) Improvement in perioperative outcome after hepatic resection: analysis of 1803 consecutive cases over the past decade. *Ann Surg* 236:397–406; discussion 406–407.
3. Dimick JB, Cowan JA, Jr, Knol JA, Upchurch GR, Jr. (2003) Hepatic resection in the United States: indications, outcomes, and hospital pro-

cedural volumes from a nationally representative database. *Arch Surg* 138:185–191.

4. Dimick JB, Wainess RM, Cowan JA, Upchurch GR, Jr, Knol JA, Colletti LM. (2004) National trends in the use and outcomes of hepatic resection. *J Am Coll Surg* 199:31–38.
5. de Jong MC, Mayo SC, Pulitano C, Lanella S, Ribero D, Strub J *et al*. (2009) Repeat curative intent liver surgery is safe and effective for recurrent colorectal liver metastasis: results from an international multi-institutional analysis. *J Gastrointest Surg* 13:2141–2151.
6. de Jong MC, van Vledder MG, Ribero D, Hubert C, Gigot JF, Choti MA *et al*. (2010) Therapeutic efficacy of combined intraoperative ablation and resection for colorectal liver metastases: an international, multi-institutional analysis. *J Gastrointest Surg* 15:336–344.
7. Abdalla EK, Hicks ME, Vauthey JN. (2001) Portal vein embolization: rationale, technique and future prospects. *Br J Surg* 88:165–175.
8. Tsai S, Marques HP, de Jong MC, Mira P, Ribeiro V, Choti MA *et al*. (2010) Two-stage strategy for patients with extensive bilateral colorectal liver metastases. *HPB* 12:262–269.
9. Abdalla EK, Denys A, Chevalier P, Nemr RA, Vauthey JN. (2004) Total and segmental liver volume variations: implications for liver surgery. *Surgery* 135:404–410.
10. Nagasue N, Yukaya H. (1989) Liver resection for hepatocellular carcinoma: results from 150 consecutive patients. *Cancer Chemother Pharmacol* 23 (Suppl.):78–82.
11. Fan ST, Lai EC, Lo CM, Ng IO, Wong J. (1995) Hospital mortality of major hepatectomy for hepatocellular carcinoma associated with cirrhosis. *Arch Surg* 130:198–203.
12. Lai EC, Fan ST, Lo CM, Chu KM, Liu CL, Wong J. (1995) Hepatic resection for hepatocellular carcinoma. An audit of 343 patients. *Ann Surg* 221:291–298.
13. Zhou L, Rui JA, Wang SB, Chen SG, Qu Q, Chi TY *et al*. (2007) Outcomes and prognostic factors of cirrhotic patients with hepatocellular carcinoma after radical major hepatectomy. *World J Surg* 31:1782–1787.
14. Nathan H, Schulick RD, Choti MA, Pawlik TM. (2009) Predictors of survival after resection of early hepatocellular carcinoma. *Ann Surg* 249:799–805.
15. Simons JP, Ng SC, Hill JS, Shah SA, Zhou Z, Tseng JF. (2010) In-hospital mortality from liver resection for hepatocellular carcinoma: a simple risk score. *Cancer* 116:1733–1738.
16. Asiyanbola B, Chang D, Gleisner AL, Nathan H, Choti MA, Schulick RD *et al*. (2008) Operative mortality after hepatic resection: are literature-based rates broadly applicable? *J Gastrointest Surg* 12:842–851.
17. Nathan H, Pawlik TM. (2008) Limitations of claims and registry data in surgical oncology research. *Ann Surg Oncol* 15:415–423.
18. Cooper GS, Virnig B, Klabunde CN, Schussler N, Freeman J, Warren JL. (2002) Use of SEER–Medicare data for measuring cancer surgery. *Med Care* 40 (Suppl. 8):43–48.
19. National Cancer Institute D, Surveillance Research Program, Cancer Statistics Branch. Surveillance, epidemiology, and end results (SEER) program. http://www.seer.cancer.gov. [Accessed 1 February 2010.]
20. Mayo SC, Shore AD, Nathan H, Edil B, Wolfgang CL, Hirose K *et al*. (2010) National trends in the management and survival of surgically managed gallbladder adenocarcinoma over 15 years: a population-based analysis. *J Gastrointest Surg* 14:1578–1591.
21. Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. (2002) Overview of the SEER–Medicare data: content, research applications, and generalizability to the United States elderly population. *Med Care* 40 (8 Suppl.):3–8.
22. Fritz AG. (2000) *International Classification of Diseases for Oncology: ICD-O*, 3rd edn. Geneva: World Health Organization.
23. Becker NS, Richardson P, Abraham NS, Anaya DA. (2010) Identification of patients with colorectal liver metastases using administrative databases. Abstracts of the Fifth Annual Academic Surgical Congress of the Association for Academic Surgery and Society of University Surgeons. San Antonio, TX, USA. 3–5 February 2010. *J Surg Res* 158:171–424.
24. Potosky AL, Warren JL, Riedel ER, Klabunde CN, Earle CC, Begg CB. (2002) Measuring complications of cancer treatment using the SEER–Medicare data. *Med Care* 40 (8 Suppl.):62–68.
25. Elixhauser A, Steiner C, Harris DR, Coffey RM. (1998) Comorbidity measures for use with administrative data. *Med Care* 36:8–27.
26. Baldwin LM, Klabunde CN, Green P, Barlow W, Wright G. (2006) In search of the perfect comorbidity measure for use with administrative claims data: does it exist? *Med Care* 44:745–753.
27. Li B, Evans D, Faris P, Dean S, Quan H. (2008) Risk adjustment performance of Charlson and Elixhauser comorbidities in ICD-9 and ICD-10 administrative databases. *BMC Health Serv Res* 8:12.
28. Quan H, Parsons GA, Ghali WA. (2002) Validity of information on comorbidity derived from ICD-9-CCM administrative data. *Med Care* 40:675–685.
29. Southern DA, Quan H, Ghali WA. (2004) Comparison of the Elixhauser and Charlson/Deyo methods of comorbidity measurement in administrative data. *Med Care* 42:355–360.
30. Kaplan EL, Meier P. (1958) Non-parametric estimation from incomplete observations. *J Am Stat Assoc* 53:457–481.
31. Thompson HH, Tompkins RK, Longmire WP, Jr. (1983) Major hepatic resection. A 25-year experience. *Ann Surg* 197:375–388.
32. Vauthey JN, Pawlik TM, Abdalla EK, Arens JF, Nemr RA, Wei SH *et al*. (2004) Is extended hepatectomy for hepatobiliary malignancy justified? *Ann Surg* 239:722–730; discussion 730–732.
33. de Jong MC, Mayo SC, Pulitano C, Lanella S, Ribero D, Strub J *et al*. (2009) Repeat curative intent liver surgery is safe and effective for recurrent colorectal liver metastasis: results from an international multi-institutional analysis. *J Gastrointest Surg* 13:2141–2151.
34. Kishi Y, Abdalla EK, Chun YS, Zorzi D, Madoff DC, Wallace MJ *et al*. (2009) Three hundred and one consecutive extended right hepatectomies: evaluation of outcome based on systematic liver volumetry. *Ann Surg* 250:540–548.
35. Gold JS, Are C, Kornprat P, Jarnagin WR, Gonen M, Fong Y *et al*. (2008) Increased use of parenchymal-sparing surgery for bilateral liver metastases from colorectal cancer is associated with improved mortality without change in oncologic outcome: trends in treatment over time in 440 patients. *Ann Surg* 247:109–117.
36. Fortner JG, Lincer RM. (1990) Hepatic resection in the elderly. *Ann Surg* 211:141–145.
37. Nagasue N, Kohno H, Chang YC, Taniura H, Yamanoi A, Uchida M *et al*. (1993) Liver resection for hepatocellular carcinoma. Results of 229 consecutive patients during 11 years. *Ann Surg* 217:375–384.
38. Carroll JE, Smith JK, Simons JP, Murphy MM, Ng SC, Shah SA *et al*. (2010) Redefining mortality after pancreatic cancer resection. *J Gastrointest Surg* 14:1701–1708.
39. Belghiti J, Hiramatsu K, Benoist S, Massault P, Sauvanet A, Farges O. (2000) Seven hundred forty-seven hepatectomies in the 1990s: an update to evaluate the actual risk of liver resection. *J Am Coll Surg* 191:38–46.
40. Choti MA, Sitzmann JV, Tiburi MF, Sumetchotimetha W, Rangsin R,

Schulick RD *et al*. (2002) Trends in longterm survival following liver resection for hepatic colorectal metastases. *Ann Surg* 235:759–766.

41. Imamura H, Seyama Y, Kokudo N, Aoki T, Sano K, Minagawa M *et al*. (2004) Single and multiple resections of multiple hepatic metastases of colorectal origin. *Surgery* 135:508–517.
42. Kanematsu T, Furui J, Yanaga K, Okudaira S, Shimada M, Shirabe K. (2002) A 16-year experience in performing hepatic resection in 303 patients with hepatocellular carcinoma: 1985–2000. *Surgery* 131 (1 Suppl.):153–158.
43. Torzilli G, Makuuchi M, Inoue K, Takayama T, Sakamoto Y, Sugawara Y *et al*. (1999) No-mortality liver resection for hepatocellular carcinoma in cirrhotic and non-cirrhotic patients: is there a way? A prospective analysis of our approach. *Arch Surg* 134:984–992.
44. Dickersin K, Min YI. (1993) Publication bias: the problem that won't go away. *Ann N Y Acad Sci* 703:135–146; discussion 146–148.
45. Dickersin K, Chan S, Chalmers TC, Sacks HS, Smith H, Jr. (1987) Publication bias and clinical trials. *Control Clin Trials* 8:343–353.
46. Cho SW, Steel J, Tsung A, Marsh JW, Geller DA, Gamblin TC. (2011) Safety of liver resection in the elderly: how important is age? *Ann Surg Oncol* 18:1088–1095.
47. Roland M. (2004) Linking physicians' pay to the quality of care – a major experiment in the United Kingdom. *N Engl J Med* 351:1448–1454.